REMARKS

Claims 1-11 and 13-19 are currently pending. Claims 15-19 are withdrawn from consideration. Claims 1 and 11 have been amended. Claims 2 and 12 have been cancelled. There being no issue of new matter, entry of the foregoing amendments is respectfully requested.

Claim Objections

The Examiner objected to claim 1 because of a typographical error in the spelling of the term "bacteranemia." Correction has been made to the term "bacteraemia."

Claim Rejections 35 U.S.C §112, Written description

The Examiner rejected claim 11 as failing to comply with the written description requirement. In particular, the Examiner asserts that there is insufficient written description for the phrase "physiological activators of inhibitors of the clotting system and their recombinant analogs." While the applicant does not agree with the Examiner's position in the interest of advancing prosecution the applicant has amended the claim to incorporate the markush group of dependent claim 12 to recite the following markush group: Protein C, recombinant human activated Protein C, TFPI and antithrombin. Claim 12 has been cancelled.

Claim Rejections under 35 U.S.C §112, Enablement

The Examiner rejected claims 1-6, 11 and 12 on the basis that the specification fails to enable claims directed to the use of the specified antithrombic compounds for *prevention* of SIR, Sepsis and bacteraemia. While the applicant does not agree with the Examiners position it has amended the claims to remove the term "prevention." Applicant requests that this basis for rejection be withdrawn.

Claim Rejections 35 U.S.C §103

The Examiner rejected claims 1-6, 11 and 12 as being unpatentable over Ries et al., in view of Rominsch et al, Tsukada et al. and Iqbal et al. and further in view of the Merck Manual regarding bacteraemia. The Examiner asserts that the compounds encompassing the elected compounds are known as antithrombotic pharmaceutical agents. The Examiner further asserts that Rominsich and Tsukada disclose that antithrombotic agents have been known to be useful in the treatment of sepsis. The Examiner asserts that a person of ordinary skill in the art would have been motivated to employ the subject compounds for the treatment of sepsis including the patients suffering from bacteraemia because antithrombotic agents were known to be useful in treating sepsis. The applicant respectfully submits that the Examiner has failed to make a prima facie case of obviousness. To establish a prima facie case of obviousness, the Examiner must show that the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated someone skilled in the art to modify a reference or combine references. *See Karsten Mfg. Corp. v. Cleveland Gulf Co. 242 F.3d 1376, 1385 (Fed. Cir. 2001).* In addition the proposed modification in the prior art must have had a reasonable expectation of success. *Amgen Inc. v. Chugai Pharm. Co. 927 F.2d 1200, 1209 (Fed. Cir. 1991).* The prior art combination of references must also teach or suggest all the limitations of the claims. *See In re Wilson 424 F.2d 1382, 1385 (C.C.P.A 1970).*

While the applicant submits that the Examiner has failed to make a prima facie case of obviousness against the claims as filed, in the interest of advancing prosecuting of the case applicant has amended the claims such that they are directed to a method employing a specific benzimidazole compound rather than the genus of compounds according to formula I. Applicant respectfully submits that the combination of cited references clearly do not provide a basis for a prima facie case of obviousness against the instant claims. The prior art combination of references coupled with the knowledge generally available at the time clearly would not have motivated someone skilled in the art to modify or combine the cited references to practice a *method for treating diseases selected from the group consisting of systemic inflammatory response syndrome (SIRS), sepsis and bacteranemia which*

comprises administering to a patient in need thereof a therapeutically effective amount of (R)-2-(4-amidinophenylaminomethyl)-*1-methyl-5-[1-(carboxymethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole optionally in the form of the pharmaceutically acceptable acid addition salts thereof, and optionally in the form of the hydrates or solvates thereof.* For convenience the term "(R)-2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(carboxymethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole optionally in the form of the pharmaceutically acceptable acid addition salts thereof, and optionally in the form of the hydrates or solvates thereof" will be referred to hereinafter as the "compound of formula (IIa)."

The Examiner asserts that Rominsch and Tsukada and Iqbal disclose that antithrombotic agents are useful for treatment of sepsis. The Examiner broadly points to abstracts and the claims of Tsukada et al. and Rominisch and the abstract of Iqbal et al. to support this premise. However, the cited references clearly fail to teach or suggests the use of the compound of formula IIa which has the property of inhibiting thrombin and factor X directly. The Examiner points to Rominisch (Col. 1-2) and Iqbal (pages 111-115) which show that microvascular thrombosis and disseminated intravascular coagulation are common symptoms from sepsis, however a showing that coagulation is a common symptom of sepsis does not establish or support the premise that the instantly recited benzimidazole compound would be useful for treating sepsis. Likewise, the Examiner's position fails to provide a basis why someone skilled in the art would have an expectation of success of treating sepsis by administration of the recited benzimidazole compound.

Applicant further submit that the cited references or combinations thereof would not lead some someone skilled in the art at the time of the invention to the instantly recited invention. In fact the cited references teaches away from the method of the instant invention.

Rominsch and Tsukada and Iqbal teach away from the instantly claimed invention

- European patent application EP 0 781 558 A2 by Tsukada et al. teaches away from the method of the invention as instantly claimed. Tsukada describes the use of heparin cofactor II in the potential treatment of infectious disease, particularly sepsis and a variety of other diseases accompanied by thromboses. The reference discloses heparin cofactor II as a plasma glycoprotein which is known to inhibit thrombin *mainly in the presence of dermatan sulphate and/or a large quantity of heparin.* The compound according to formula (IIa) has been evaluated in an animal model using purified LPS (Lipopolysaccharide) in order to simulate an inflammatory response (see Example 2 of the specification, page 36). This experimental model seeks to reflect the systemic inflammatory response syndrome which can be related to a variety of stimuli rather than an infectious model mimicking the particular aspects of sepsis, i.e. the infectious disease related aspects. Importantly, the claimed compound was shown to reduce organ damage in this model so that it can be concluded that the use of the compound of formula (IIa) is not related to infectious agents as in sepsis but to SIRS in general. Therefore, the results with the compound of formula (IIa) in a model without an infectious agent would not have been expected. While Tsukada teaches a role of heparin in the treatment of sepsis there is no teaching or suggestion to use a benzimidazole compound such as a compound according to formula (IIa) claimed compound for the treatment of sepsis.

As compared to heparin cofactor II, the compound according to formula (IIa) is a direct inhibitor of thrombin and factor Xa. There is no interaction with dermatan sulphate or heparin. Consequently, someone skilled in the art would not have any motivation to use the claimed compound in the instant claims for the treatment of sepsis.

The compound of formula (IIa) has shown efficacy in a model of inflammation clearly distinct from a sepsis, i.e. infectious disease model. Furthermore, the effect is related to its direct activity against thrombin and factor Xa and is not related to either effects on inflammatory cytokines or interaction with heparin or dermatan sulphate.

- *Iqbal et al.* (Expert Opinions Emerging Drugs 2002, 7, 111-139) teaches away from the method of the claimed invention. Iqbal describes the use of anticoagulants in the

treatment of severe sepsis. The reference discusses sepsis as inflammatory response to a microbial agent and highlights the role of bacteria in sepsis, particularly with regard to the differences between gram-negative and gram-positive sepsis and respective predisposing factors. The reference highlights the role of the immune system for the response to infection and proposes various inflammatory mediators as targets for sepsis treatment. The reference also describes the role of activated coagulation in severe sepsis. The reference proposes the use of anticoagulants in the treatment of sepsis. The proposal is based on the rationale that since intravascular thrombi and disseminated intravascular coagulation in humans with severe sepsis is present that the coagulation system is activated. The reference describes anticoagulants which are currently in use or in development as potential treatments for severe sepsis and describe the results of three clinical development programmes for activated protein C, antithrombin and TFPI. Of the three the only successful one was activated protein C (APC) programme. For all three, an additional anti-inflammatory mechanism has been proposed which is also reflected in this overview which gives thorough details how APC interactions with inflammation via the EPC-receptor.

- European patent application EP 1 027 894 A2 by Dickneite et al. teaches away from the method of the invention because it describes the use of antithrombin for the treatment of inflammatory processes being accompanied by an increased distribution of cytokines and/or tissue factor. The reference highlights the anti-inflammatory properties of antithrombin which are distinct from its anti-thrombin and anti-clotting capability (See Col. 1, line 55-57). The reference teaches that Antithrombin III is not acting as an anticoagulant but may affect the signalling mechanism for regulation of the proinflammatory cytokines (See Col. 2, lines 17-20). This rationale is consistent with the prevailing knowledge and expectations in the art that an increase of inflammatory mediators is the primary reason for organ dysfunction and failure in sepsis. The compound according to formula (IIa) the invention is a pure anticoagulant inhibiting thrombin and factor Xa directly. Therefore, it has no direct anti-inflammatory effects. Consequently, this reference teaches away from employing a method the employs compounds which have the property of inhibiting thrombin and factor X directly.

Authorization for payment of fees for a three month extension of time for reply to the Office Action is hereby given. It not believed that any other fees are required beyond those that may otherwise be provided for in accompanying documents. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. §1.136(a) and any fees required therefore are hereby authorized to be charged to our Deposit Account No. 02-2955.

If any points remain at issue which can best be resolved by way of a telephonic or personal interview, the Examiner is kindly requested to contact the undersigned attorney at the local telephone number listed below

Respectfully submitted,

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